REMARKS/ARGUMENTS

Claims 1-3, 5, 7-9, 11, 12, 14, 15, 18-20 and 22-25 are pending in this application. In a non-final Office Action mailed June 6, 2007, the Patent Office rejected all of the pending claims. Claims 2, 18-20 and 24 are canceled by the present amendment; the rejections as applied to these claims are therefore moot. The canceled claims will not be addressed further herein.

I. Rejection Under 35 U.S.C. § 102(b)

A. Basis for the rejection

Presently pending claims 1, 3, 5, 7-9, 11, 12, 14, 15, 22 and 23 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,763,394 ("O'Connor et al."). The following remarks address this rejection as it relates to previously pending claims, and as it may relate to new claim 26. The applicants do not dispute the Patent Office's characterization of the claims. The Patent Offices characterizes O'Connor et al. as disclosing a human growth hormone formulation consisting essentially of (a) 1 mg/ml to 20 mg/ml human growth hormone (hGH), (b) a preservative, (c) a buffer system to provide a pH of 5.5 to 7, (d) 0.1 % w/v to 1% w/v non-ionic surfactant, and (e) 50 mM to 200 mM neutral salt. Office Action, page 3. According to the Patent Office, O'Connor et al. also discloses that

- the buffer be selected from the group consisting of citrate, phosphate and acetate buffers;
- the buffer is most advantageously in the range of about 2 mM to about 50 mM;
- the non-ionic surfactant is poloxamer 188, poloxamer 184, or polysorbate;
- the preferred preservatives include 0.2-0.4 % w/v phenol;
- inclusion of about 5 mg/ml to about 50 mg/ml mannitol, as opposed to neutral salts.

Office Action, pages 3-4. The Patent Office also states that O'Connor et al. disclose a directly injectable formulation consisting essentially of (a) 5 mg/ml hGH, (b) 0.5 mg/ml phenol, (c) 2.5 mg/ml sodium citrate (aqueous buffer), (d) 2.0 mg/ml polysorbate 20 (non-ionic surfactant), and (e) 8.8 mg/ml sodium chloride (neutral salt/isotonicity agent), and further discloses an hGH formulation containing (a) 5 mg/ml hGH, (b) 0.25 w/v phenol, (c) 10 mg/ml sodium citrate (aqueous buffer), (d) 0.1 % w/v poloxamer 188 (non-ionic surfactant), and (e) 50 mM mannitol (tonicity adjusting agent). Office Action, page 4. Finally, the Patent Office states that O'Connor et al. discloses that the neutral salts concentration is adjusted to near isotonicity, depending on the other ingredients in the formulation. *Id.*

Based on the foregoing, the Patent Office concludes that O'Connor et al. fully anticipates each of pending claims 1, 3, 5, 7-9, 11, 12, 14, 15, 22 and 23. Office Action, page 4.

B. Applicants' response

The applicants respectfully submit that the Patent Office has not established anticipation of the presently pending claims by O'Connor et al.

O'Connor et al. discloses liquid formulations of hGH that include *at least* either a neutral salt or mannitol. Although O'Connor et al. states in the Summary of the Invention that

> One aspect of the invention is a stable, pharmaceutically acceptable, aqueous formulation of human growth hormone comprising human growth hormone, a buffer, a non-ionic surfactant, and *optionally*, a neutral salt, mannitol and a preservative [col. 2, lines 28-32 (emphasis added)

In fact, all of the formulations disclosed in O'Connor et al. contain *either* mannitol *or* a neutral salt, with preferred embodiment of the disclosed formulations *consist of* or *consisting essentially of* hGH, nonionic surfactant, buffer and *either* a neutral salt *or* mannitol (e.g., col. 5, lines 7-14, Example IV, claims 1, 9, 18, 20, 21 and 23, Table 3). While O'Connor et al. state in passing that [t]he inclusion of the non-ionic surfactant is the most important factor in preventing this phenomenon from occurring" (col. 6, lines 42-44), there is no basis for concluding either that the inclusion of the non-ionic surfactant is alone sufficient, or that the inclusion of either mannitol or a neutral salt is not required, to achieve the beneficial results of the invention, because all of the test data was obtained using formulations that additionally included either mannitol or a neutral salt. In fact, the conclusion is just the opposite, as every exemplification of the O'Connor et al. formulations, and every claim directed thereto, require the presence of either mannitol or a neutral salt. Furthermore, there is no disclosure of an hGH formulation having a tonicity of from about 100 mos/kg to about 500 mos/kg.

In contrast, the present claims are all directed to formulations *consisting essentially of*

(a) hGH in an amount of from about 5 mg/ml to about 100 mg/ml;

(b) phenol;

(c) an aqueous buffer; and

(d) a non-ionic surfactant

which *additionally* must have a tonicity of from about 100 mos/kg to about 500 mos/kg, must have a pH in the narrow range of from about 6.1 to about 6.3, and must be substantially free of an amino acid excipient. By use of the narrowing language "consisting essentially of," the present claims preclude the presence of addition excipients such as a neutral salt and/or mannitol, which as explained above are necessary components of the O'Connor et al. formulations. Furthermore, though O'Connor et al. "[t]he *salt concentration* is adjusted to near *isotonicity*" (col. 4, line 3), there is no disclosure of formulations having a possible *range* of tonicity of from about 100 mos/kg to about 500 mos/kg, in the *absence* of a salt, as required by the presently pending claims.

The foregoing establishes that O'Connor et al. does not, in fact, disclose each and every element of the present claims, and therefore cannot anticipate the claimed invention. The

applicants therefore respectfully submit that the rejection under 35 U.S.C. § 102(b) of claims 1, 3, 5, 7-9, 11, 12, 14, 15, 22 and 23 over O'Connor et al. can properly be withdrawn, and further than new claim 26 is not anticipated by O'Connor et al. Withdrawal of this rejection is respectfully requested.

II. Rejection Under 35 U.S.C. § 103(a)

A. Basis for the rejection of claim 1

Presently pending claims 1 and 25 were rejected under 35 U.S.C. § 103(a) as being obvious over O'Connor et al. The following remarks address this rejection as it relates to presently pending claims 1 and 25, and as it may relate to new claim 26. The Patent Office states that the subject claims are directed to formulations that consist essentially of (a) 6.7 mg/ml hGH, (b) 2.5 mg/ml phenol, (c) 10 mM sodium phosphate buffer (aqueous buffer), (d) 30 mg/ml mannitol (tonicity agent, and (e) 2 mg/ml poloxamer 188 (non-ionic surfactant), wherein the formulation is at a pH of 6.2. Office Action, page 6. This characterization of the claims is incorrect and incomplete. Not all of the subject claims recite mannitol, and the presently pending claims specifically exclude additional excipients such as mannitol by use of the "consisting essentially of" language. Furthermore, each claim includes the further element that the formulation have a tonicity of from about 100 mos/kg to about 500 mos/kg, and being free of an amino acid excipient. Finally, claim 1 is not limited to the amounts of excipient stated in the Patent Office's characterization of the claims.

With respect to the rejection of claim 1 (and to the extent it may apply to it, new claim 26), the Patent Office asserts that O'Connor et al. discloses formulations consisting essentially of

(a) from about 1 mg/ml to about 20 mg/ml hGH,

(b) 0.2-0.4% (w/v) phenol,

(c) from about 2 mg/ml to about 50 mM buffer, including phosphate buffer,

(d) from about 0.1% (w/v) to about 5% (w/v non-ionic surfactant, including poloxamer 188; and

(e) from about 5 mg/ml to about 50 mg/ml mannitol,

wherein the formulations have a pH of from about 5.5 to about 7. On this basis, the Patent Office concludes that presently pending claim 1, as characterized by the Patent Office, would have been *prima facie* obvious to one skilled in the art at the time of the invention, because O'Connor et al. teaches each of the components of the hGH formulation with the suitable ranges that overlap the components of the presently pending claims. Office Action, page 7.

B. Applicants' response

On the contrary, there is no teaching in O'Connor et al. that would have been lead to the formulation of claim 1. O'Connor et al. nowhere suggests utilization of the particular amounts of

each component to create the liquid hGH formulation recited in claim 1, and in new claim 26. Furthermore, as established above with respect to the rejection under § 102(b), O'Connor does not teach or suggest a formulation having a tonicity of from about 100 mos/kg to about 500 mos/kg. Finally, O'Connor et al. does not teach or suggest the formulation of the presently pending claims 1 and 26, which *omits* mannitol. Because the Patent Office has not established that it would have been *prima facie* obvious to select and combine in a formulation each of the recited elements of claim 1 (and to the extent this rejection might apply to it, new claim 26), in the specified amounts, and adjust the tonicity of the formulation to from about 100 mos/kg to about 500 mos/kg, a case for the *prima facie* obviousness of claim 1 (and to the extent this rejection might apply to it, new claim 26) over O'Connor et al.

C. Basis for the rejection of claim 25

With respect to the rejection of claim 25, the Patent Office asserts that although O'Connor et al. does not specifically teach a kit comprising a hGH formulation, "O'Connor et al. do teach a method for using their hGH formulation comprising formulating their composition in a pharmaceutically acceptable, injectable sterile aqueous vehicle, storing said formulation, and directly injecting the stored formulation into a patient." Office Action, page 8. On this basis, the Patent Office concludes that it would have been *prima facie* obvious for one skilled in the art at the time of the invention to prepare a kit as recited in claim 25,

> because O'Connor et al. teach storing their hGH formulation followed by injecting the formulation into a patient. Thus, the method taught by O'Connor et al. requires the use of an injectable device and a container to store the hGH formulation.

Office Action, page 8.

D. Applicants' response

Applicants submit that this rejection is unfounded. Claim 25 recites "[a] *kit* comprising an injection device *and* a separate container containing a multi-dose liquid formulation of human growth hormone *according to claim 1*" (emphasis added). First, as established above, O'Connor does not teach or suggest a human growth hormone formulation according to claim 1, and in fact the teaching referred to by the Patent Office relates to the use of materially *different* formulations (ones containing a neutral salt). For this reason alone, the present rejection is unfounded. Second, to the extent that the method taught in O'Connor et al. could be considered to require the use of an injectable device and a container to store the hGH formulation, there is nothing to suggest that these are presented as a *kit* as required by claim 25, nor has the Patent Office established that a person skilled in the art would have necessarily lead to such a kit based solely on the statement in O'Connor et al. that a different hGH formulation could be hGH is stored, and subsequently injected into a patient. A kit as recited in claim 25, comprising a container with multiple doses of hGH and an injection device, is a particularly advantageous

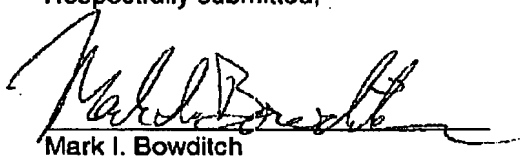
combination, as it simplifies self-administration of hGH by persons who are not medical professionals (*c.f.*, instant specification, page 2, second full paragraph; paragraph bridging pages 6 and 7; page 7, first and second full paragraphs). If something as advantageous as the kit recited in claim 25 were contemplated by O'Connor et al., it surely would have been referred to in some way.

The foregoing establishes that O'Connor et al. does not teach or suggest each and every element of presently pending claims 1 and 25, and that the Patent Office has failed to establish a case that those claims are *prima facie* obvious. The applicants therefore respectfully submit that the rejection under 35 U.S.C. § 103(a) of claims 1, 25 and 26 can properly be withdrawn, and furthermore that this rejection is inapplicable to new claim 26. Withdrawal of these rejections is respectfully requested.

CONCLUSION

In view of the foregoing, the applicants respectfully submit that the claims are free of the prior art, and in condition for allowance, and that the pending rejections can properly be withdrawn. Favorable action on the claims is earnestly solicited

Respectfully submitted,



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